

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 05 June 2001 (05.06.01)	
International application No. PCT/AU00/01056	Applicant's or agent's file reference 7525400
International filing date (day/month/year) 06 September 2000 (06.09.00)	Priority date (day/month/year) 06 September 1999 (06.09.99)
Applicant HEATON, Andrew et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 06 April 2001 (06.04.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nestor Santesso
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

TENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

REC'D 28 DEC 2001

WIPO PCT

12

Applicant's or agent's file reference 7525400	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/AU00/01056	International Filing Date (<i>day/month/year</i>) 6 September 2000	Priority Date (<i>day/month/year</i>) 6 September 1999
International Patent Classification (IPC) or national classification and IPC Int. Cl. ⁷ C07D 311/36, 311/38, 471/06; C07C 49/215, 49/213; A61K 31/352, 31/12, 21/437; A61P 5/00, 5/22, 25/24, 9/10, 19/10, 19/02, 17/06, 7/00, 35/00, 25/28, 17/04, 1/00		
Applicant NOVOGEN RESEARCH PTY LTD et al		

1.	This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2.	This REPORT consists of a total of 7 sheets, including this cover sheet. <input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheet(s).
3.	This report contains indications relating to the following items: I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application

Date of submission of the demand 6 April 2001	Date of completion of the report 18 December 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer K. LEVER Telephone No. (02) 6283 2254

I. Basis of the report**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed.
- ☐ the description, pages , as originally filed,
 pages , filed with the demand,
 pages , received on with the letter of
- ☐ the claims, pages , as originally filed,
 pages , as amended (together with any statement) under Article 19,
 pages , filed with the demand,
 pages , received on with the letter of
- ☐ the drawings, pages , as originally filed,
 pages , filed with the demand,
 pages , received on with the letter of
- ☐ the sequence listing part of the description:
 pages , as originally filed
 pages , filed with the demand
 pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos: **1,2,4-9 in part and claims 10 and 11 in full.**

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☒ the claims, or said claims Nos. **1,2,4-9 in part** are so inadequately supported by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for said claim Nos. **10 and 11 because there was no support in the specification.**

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims	YES
	Claims 1-9	NO
Inventive step (IS)	Claims	YES
	Claims 1-9	NO
Industrial applicability (IA)	Claims 1-9	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

Citations:

1. Aust. J. Chem., Volume 31, No: 2, Issued 1978, Lamberton et al, "Catalytic hydrogenation of Isoflavones", pages 455-7. See in particular page 456 compounds 1, 4,8,9 and 10.
2. Phytochemistry, vol 29 No 3, Issued 1990, Weidenborner et al, "Antifungal activity of isoflavonoids..." pages 801-3. See page 802 compounds B₁, B₂, B₃, D₃, G₃, H₃, I₃
3. Aust. J. Chem., Volume 34, No 12, issued 1981, Liepa et al, "A synthesis of hydroxylated isoflavylum....", pages 2647-55. See page 2649 compounds 4a, 9a, 9b, 9d, 9f, 10a, 10b, 10c.
4. J. Electrochem. Soc. India, Volume 47, No. 4, issued 1998, Bannerjee et al, "Polarography of flavanone and isoflavanone", pages 237-244. See page 239.
5. Heterocycles, Volume 28, No.1, issued 1989, Wahala et al, "Hydrogen transfer reduction of Isoflavones", pages 183-186. See page 185.
6.) WO 99/36050 A1 (NOVOGEN RESEARCH PTY. LTD.) publication date 22 July 1999. See formulas 1 and 2 on page 6 and compounds 17-19.
7. ✓ WO 99/18953 A1 (CHILDREN'S HOSPITAL OAKLAND RESEARCH INSTITUTE) publication date 22 April 1999. See document in general and compounds on page16 Table II.
8.) WO 98/08503 A1 (NOVOGEN RESEARCH PTY.LTD.) publication date 5 March 1998. See whole document.
9.) WO 98/48790 A1 (ANTICANCER INC.) publication date 5 November 1998. See whole document.
10. FR 2693724 A1 (LYONNAISE INDUSTRIELLE PHARMACEUTIQUE) publication date 21 January 1994. See example 1 and 2.
11. US 4157984 (ZILLIKEN) publication date 12 June 1979. See formula I, column 4 line 30, column 2 lines 10-19 and the abstract.
12. DE 4432947 A1 (NEW STANDARD GmbH) publication date 21 March 1996. See column 2

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V 2**Explanations.**

So many documents were cited because they all disclosed different compounds or aspects that fall within the scope of the present claims. This was only a selection of documents found in the search, other documents were not cited because they disclosed the same compounds as the above documents. In general the citations above will direct the applicant to the particular compounds which fall within the scope of the claims. Therefore I will only discuss a sample of the cited documents.

WO 98/08503 generically discloses the compounds of claim 1 while the exemplified compounds are excluded from the claims by provisos. The document discloses the use of these compounds as therapeutic agents for diseases and conditions as claimed in the present invention. Food and drink products containing these compounds are also disclosed.

FR 2693724 example 1 of this document is identical to example 5 and a compound of claim 3 in the current invention. This document also has generic disclosure of the compounds claimed in claim 2 of the present invention.

US 4157984 discloses compounds falling within the scope of claim 2 of the present invention, it also discloses the treatment/prevention of atherosclerosis. Foodstuffs containing the compounds of the invention are also contemplated.

Claims 1-9 are not considered novel or to possess an inventive step in light of the above cited documents.

Claims 1-9 are considered to be Industrially Applicable.

VI. Certain documents cited**1. Certain published documents (Rule 70.10)**

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 00/03707	(27/01/2000)	(13/07/1999)	(15/07/1998)

This document discloses compounds falling within the scope of claim 1 and would impact on the novelty of that claim if the priority date was at a later point found to be not valid.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
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VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 3 is not clear. Claim 3 is appended to claim 1. Example 15, which is the last compound on page 35, has been excluded from claim 1 by the 1st proviso.

Claim 1 is not clear because where W is R1 and A and B are taken together to form a six membered ring the 2nd option appears not to be an isoflavone because the y is not present.

The claims in general are broad and largely unsupported by the description or examples.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/01056

A. CLASSIFICATION OF SUBJECT MATTER				
Int. Cl. ⁷ : C07D 311/36, 311/38, 471/06, C07C 49/215, 49/ 213, A61K 352, 31/12, 31/437, A61P 5/00, 25/22, 25/24, 9/10, 19/10, 19/02, 17/06, 7/00, 35/00, 25/28, 17/04, 1/00 According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED				
Minimum documentation searched (classification system followed by classification symbols)				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN substructure search, Isoflavone backbone ; CA chemical name search of examples.				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	Aust. J. Chem., Volume 31, No: 2, Issued 1978, Lamberton et al, "Catalytic hydrogenation of Isoflavones", pages 455-7. See in particular page 456 compounds 1, 4,8,9 and 10.	1, 3		
X	Phytochemistry, vol 29 No 3, Issued 1990, Weidenborner et al, "Antifungal activity of isoflavonoids..." pages 801-3. See page 802 compounds B ₁ , B ₂ , B ₃ , D ₃ , G ₃ , H ₃ , I ₃	1, 2		
X	Aust. J. Chem., Volume 34, No 12, issued 1981, Liepa et al, "A synthesis of hydroxylated isoflavylum....", pages 2647-55. See page 2649 compounds 4a, 9a, 9b, 9d, 9f, 10a, 10b, 10c.	1, 3		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex				
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="vertical-align: top;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>			
Date of the actual completion of the international search 15 November 2000		Date of mailing of the international search report 27 NOV 2000		
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929		Authorized officer K. LEVER Telephone No : (02) 6283 2254		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU00/01056

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Electrochem. Soc. India, Volume 47, No. 4, issued 1998, Bannerjee et al, "Polarography of flavanone and isoflavanone", pages 237-244. See page 239.	1
X	Heterocycles, Volume 28, No.1, issued 1989, Wahala et al, "Hydrogen transfer reduction of Isoflavones", pages 183-186. See page 185.	1
X	WO 99/36050 A1 (NOVOGEN RESEARCH PTY. LTD.) publication date 22 July 1999. See formulas 1 and 2 on page 6 and compounds 17-19.	1
X	WO 99/18953 A1 (CHILDREN'S HOSPITAL OAKLAND RESEARCH INSTITUTE) publication date 22 April 1999. See document in general and compounds on page 16 Table II.	1, 2
X	WO 98/08503 A1 (NOVOGEN RESEARCH PTY. LTD.) publication date 5 March 1998. See whole document.	1, 4-9
X	WO 98/48790 A1 (ANTICANCER INC.) publication date 5 November 1998. See whole document.	1,2,4-8
X	FR 2693724 A1 (LYONNAISE INDUSTRIELLE PHARMACEUTIQUE) publication date 21 January 1994. See example 1 and 2.	1,2,3
X	Patent Abstracts of Japan, JP 1-226824 A (OTA ISAN: KK) publication date 11 September 1989. See abstract	1,2
X	US 4157984 (ZILLIKEN) publication date 12 June 1979. See formula I, column 4 line 30, column 2 lines 10-19 and the abstract.	2, 4-9
P,X	WO 00/03707 A1 (LABORATOIRE L. LAFON) publication date 27 January 2000, See examples	1
X	DE 4432947 A1 (NEW STANDARD GmbH) publication date 21 March 1996 See column 2	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU00/01056

Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: I (Unsearchable Claims)

Claims 1, 2, 4-9 have not fully been searched for economical reasons. These claims are broad and largely unsupported by the description with no examples to the majority of compounds encompassed by the claims.

Claims 10 and 11 have not been searched because there is no support for any microorganisms in the description.

Claim 3 has been fully searched.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU00/01056

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos: 1,2, 4-9 in part and claims 10 and 11 in full.
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See supplement sheet.
3. ☐ Claims Nos :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU00/01056

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
WO	99/36050	AU	16518/99	EP	1049451		
WO	99/18953	AU	10939/99	EP	1024803	US	5972995
WO	98/08503	AU	40034/97	EP	954302	GB	2331015
WO	98/48790	AU	71657/98				
JP	01226824		NO	FAMILY	MEMBERS		
US	4157984	US	4234577	EP	25783	WO	8002027
		DE	2967100	JP	56500493		
WO	00/003707	AU	46282/99	FR	2781154		
FR	2693724		NO	FAMILY	MEMBERS		
DE	4432947		NO	FAMILY	MEMBERS		
END OF ANNEX							



European Patent
Office

SUPPLEMENTARY PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 00 96 0231

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	GB 1 495 189 A (PFIZER LTD) 14 December 1977 (1977-12-14) * claim 1; example 27 *	1-8	C07D311/36 C07D311/38 C07D471/06 C07C49/215 C07C49/213
E	WO 00 62765 A (ASTRAZENECA AB ;BARLAAM BERNARD CHRISTOPHE (US); PISER TIMOTHY MAR) 26 October 2000 (2000-10-26) * claim 4; example 23 *	1-8	A61K31/12 A61K31/437 A61P5/00 A61P25/22 A61P25/24 A61K31/35
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			A61K A23L C07D

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

INCOMPLETE SEARCH

The Search Division considers that the present application, or some or all of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for the following claims:

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

1

EPO FORM 1503 03.82 (P04C20)

Place of search MUNICH	Date of completion of the search 15 April 2003	Examiner Seelmann, I
CATEGORY OF CITED DOCUMENTS		
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document		



European Patent
Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 00 96 0231

Claim(s) searched completely:
3

Claim(s) searched incompletely:
1,2,4-8

Reason for the limitation of the search:

Present claims 1 and 2 relate to an extremely large number of possible compounds. In fact, the claims contain so many options and provisos that a lack of clarity (and conciseness) within the meaning of Article 84 EPC arises to such an extent as to render a meaningful search of the claims impossible. Furthermore, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 84 EPC). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to claim 3.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO.

EP 00 96 0231

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-04-2003

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 1495189	A	14-12-1977	BE 846109 A1	10-03-1977
			DE 2640617 A1	17-03-1977
			DK 411976 A	13-03-1977
			FR 2329269 A1	27-05-1977
			JP 52057182 A	11-05-1977
			LU 75770 A1	12-05-1978
			NL 7610059 A	15-03-1977
			US 4117149 A	26-09-1978
WO 0062765	A	26-10-2000	AU 4128800 A	02-11-2000
			BG 106103 A	31-05-2002
			BR 0009814 A	08-01-2002
			CN 1358091 T	10-07-2002
			CZ 20013714 A3	14-08-2002
			EE 200100526 A	16-12-2002
			EP 1173164 A2	23-01-2002
			WO 0062765 A2	26-10-2000
			HU 0200740 A2	29-07-2002
			JP 2002542187 T	10-12-2002
			NO 20015015 A	17-12-2001
			SK 14762001 A3	08-10-2002
			TR 200201762 T2	21-10-2002
			US 6518301 B1	11-02-2003

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/17986 A1

(51) International Patent Classification?: C07D 311/36,
311/38, 471/06, C07C 49/215, 49/213, A61K 31/12,
31/437, A61P 5/00, 25/22, 25/24, 9/10, 19/10, 19/02,
17/06, 7/00, 35/00, 25/28, 17/04, 1/00

(21) International Application Number: PCT/AU00/01056

(22) International Filing Date:
6 September 2000 (06.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 6 September 1999 (06.09.1999) AU
PQ 2661

(71) Applicant (for all designated States except US): NOVO-
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(72) Inventors; and

(75) Inventors/Applicants (for US only): HEATON, Andrew

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2046 (AU). KUMAR, Naresh [AU/AU]; 33 White Av-
enue, Maroubra, NSW 2035 (AU). KELLY, Graham, Ed-
mund [AU/AU]; 47 Coolawin Street, Northbridge, NSW
2063 (AU). HUSBAND, Alan [AU/AU]; 2/18 West Cres-
cent Street, McMahon's Point, NSW 2060 (AU).

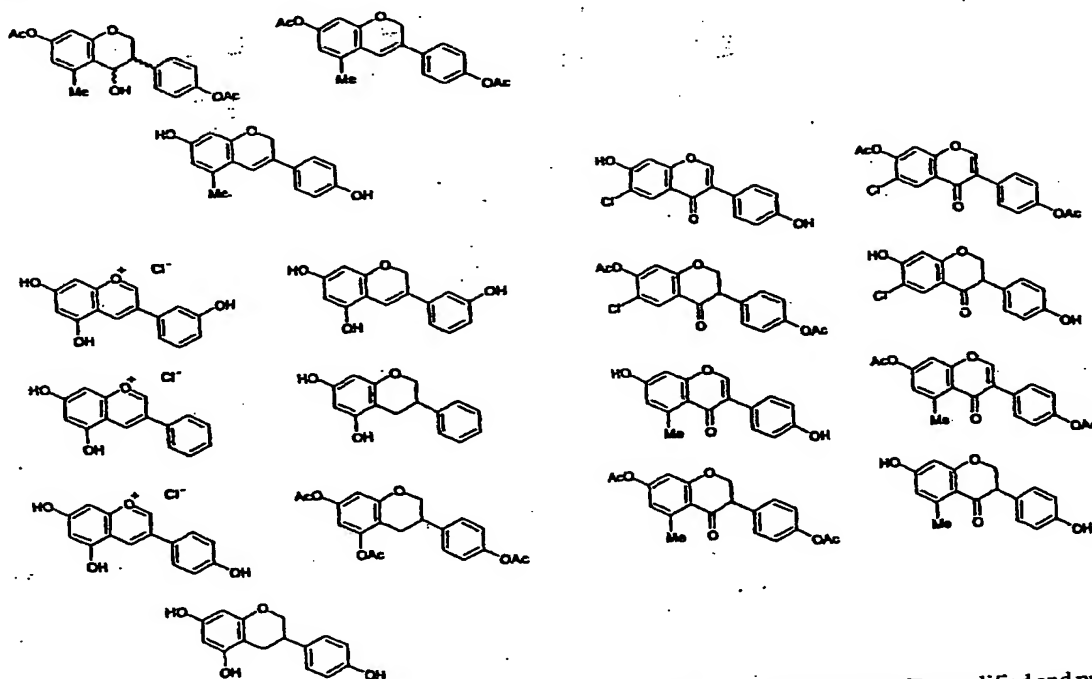
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[Continued on next page]

(54) Title: COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING ISOFLAVONES AND ANALOGUES THEREOF



(57) Abstract: Isoflavone compounds are described and recommended as therapeutic agents. Exemplified and preferred compounds are (a). Indications show compounds have good competitive binding to estrogen receptors. This is exemplified.

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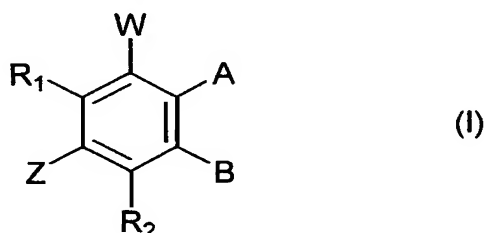
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- 1 -

COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING ISOFLAVONES AND ANALOGUES THEREOF

This invention relates to compounds, formulations, drinks, foodstuffs, methods and
5 therapeutic uses involving, containing, comprising, including and/or for preparing certain
isoflavone compounds and analogues thereof.

According to an aspect of this invention there is provided isoflavone compounds and
analogues thereof of the general formula I:



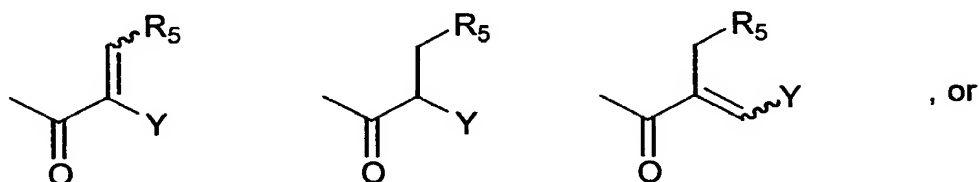
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in which

R_1 and R_2 are independently hydrogen, hydroxy, OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10} , $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

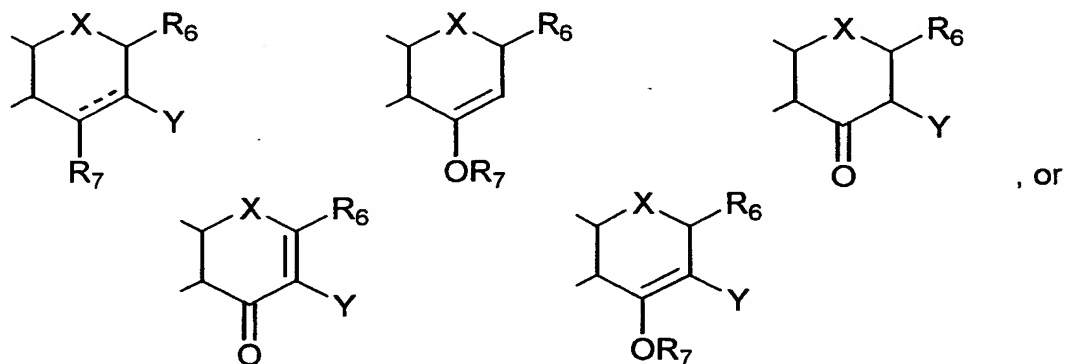
15 Z is hydrogen, and

W is R_1 , A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

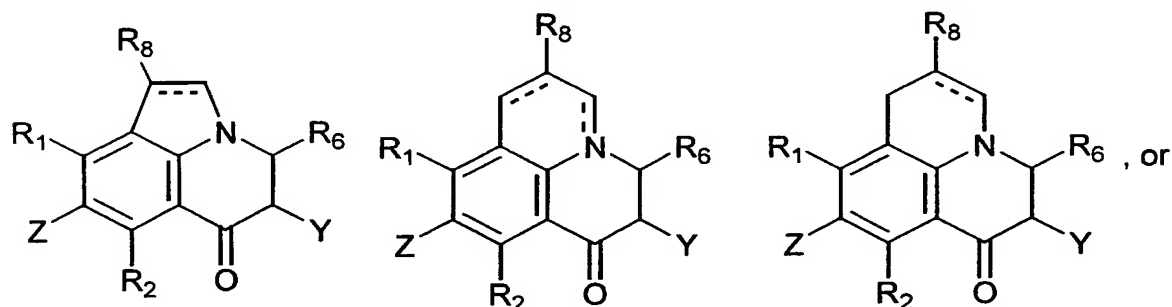


W is R_1 , and A and B taken together with the carbon atoms to which they are attached
form a six-membered ring selected from

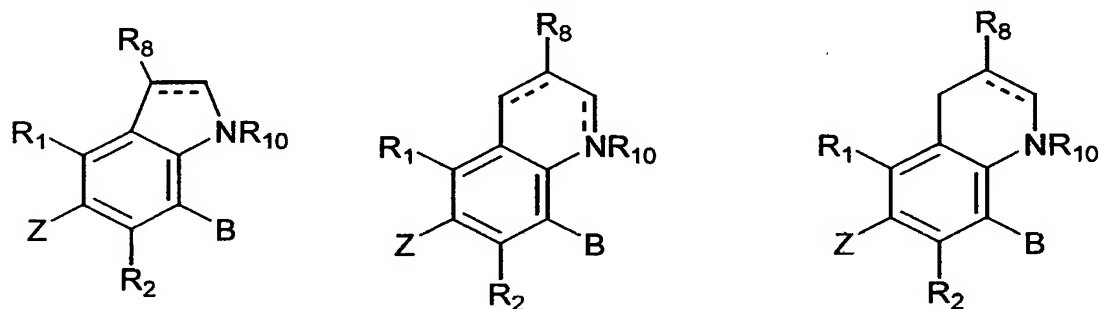
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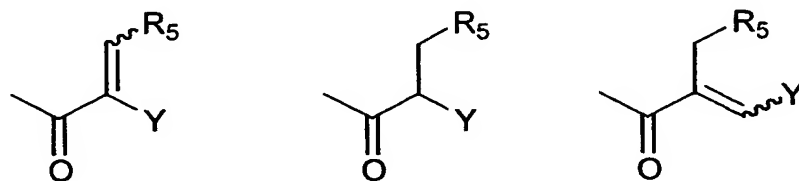
W, A and B taken together with the groups to which they are associated comprise



W and A taken together with the groups to which they are associated comprise



and B is



wherein

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R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

5 or R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

10 R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4 , COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or

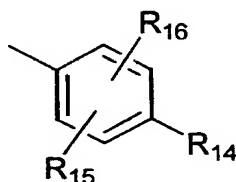
15 $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

20 Y is



wherein

R_{14} , R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10} , $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio,

25 amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that

when

- 4 -

- R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and
 R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and
 W is hydrogen, then
5 Y is not 4-hydroxyphenyl or 4-alkylphenyl;

when

- R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and
 R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as
10 previously defined, and
 Y is 4-hydroxyphenyl or 4-alkylphenyl, then
 W is not hydrogen;

when

- 15 R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and
 Y is 4-hydroxyphenyl or 4-alkylphenyl, and
 W is hydrogen, then
 R_2 is not hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined; and

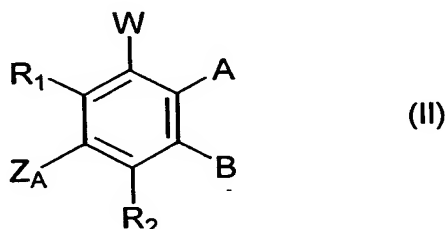
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when

- R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and
 Y is 4-hydroxyphenyl or 4-alkylphenyl, and
25 W is hydrogen, then
 R_1 is not hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid.

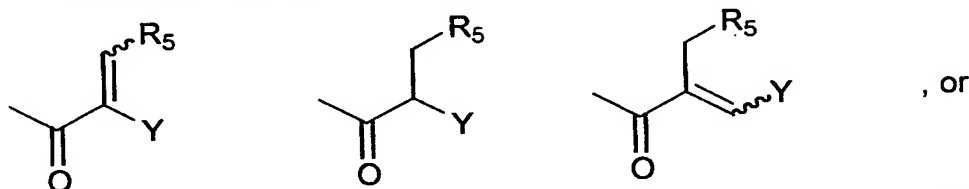
- 5 -

According to another aspect of this invention there is provided isoflavone compounds and analogues thereof of the general formula II:

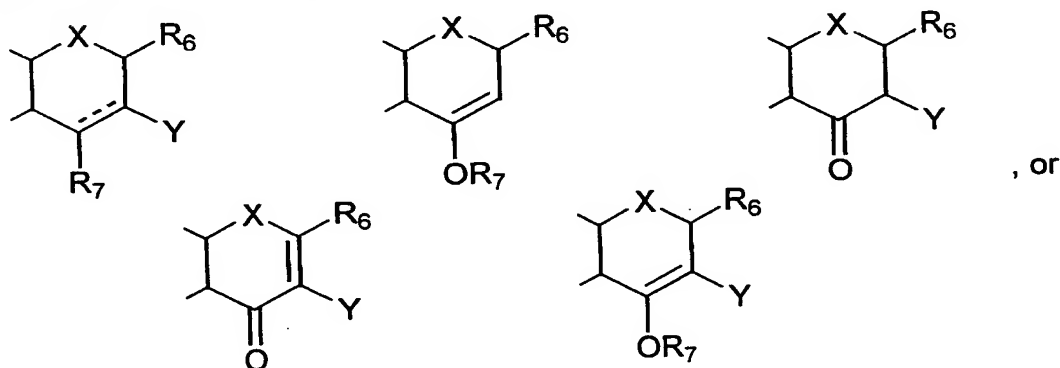


in which

- 5 R_1 and R_2 are independently hydrogen, hydroxy, OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10} , $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,
- Z_A is OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10} , $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or
- 10 halo, and
- W is R_1 , A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from



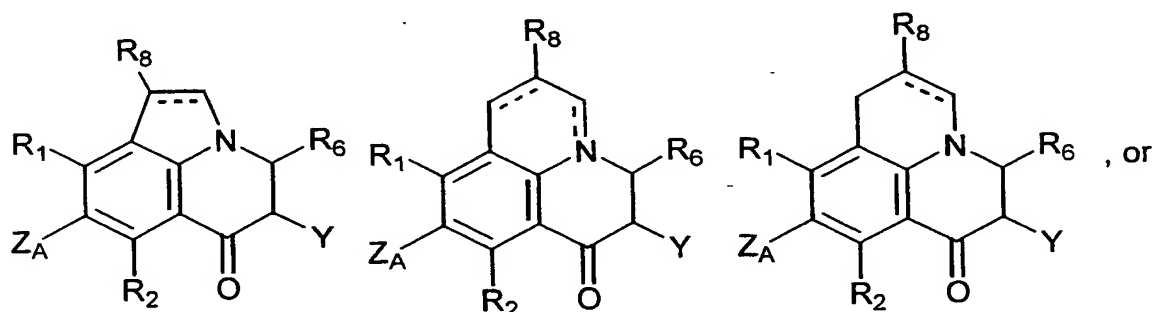
W is R_1 , and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from



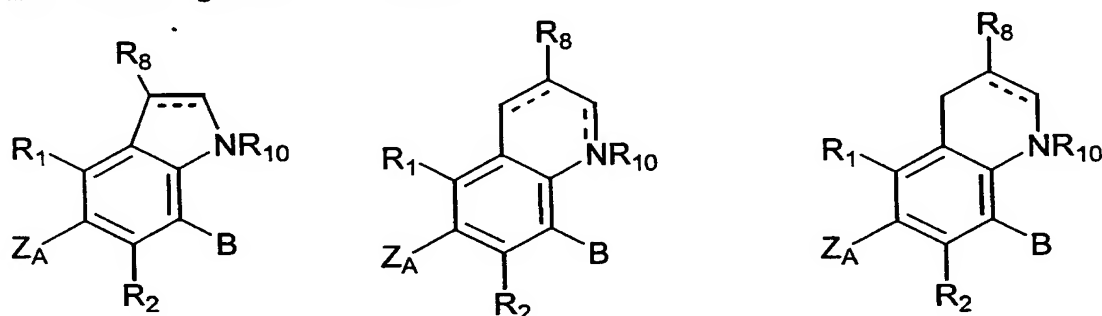
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W, A and B taken together with the groups to which they are associated comprise

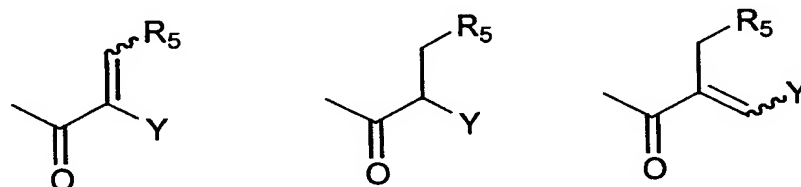
- 6 -



W and A taken together with the groups to which they are associated comprise



and B is



5

wherein

R₃ is hydrogen, alkyl, aryl, arylalkyl, an amino acid, C(O)R₁₁ where R₁₁ is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO₂R₁₂ where R₁₂ is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

10 R₄ is hydrogen, alkyl or aryl,

or R₃ and R₄ taken together with the nitrogen which they are attached are pyrrolidinyll or piperidinyll,

R₅ is hydrogen, C(O)R₁₁ where R₁₁ is as previously defined, or CO₂R₁₂ where R₁₂ is as previously defined,

15 R₆ is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR₃R₄, COR₁₁ where R₁₁ is as previously defined, CO₂R₁₂ where R₁₂ is as previously defined or CONR₃R₄,

- 7 -

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

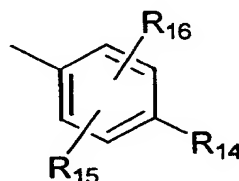
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or
 5 $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "—" represents either a single bond or a double bond,

X is O, NR_4 or S, and

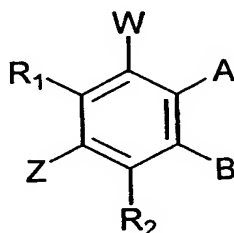
10 Y is



wherein

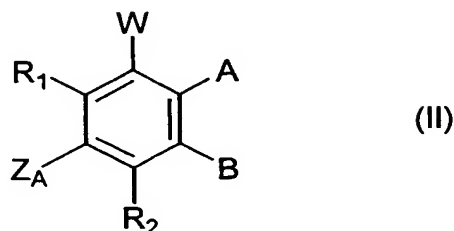
R_{14} , R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO , $C(O)R_{10}$, $COOH$, CO_2R_{10} , $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio,
 15 amino, alkylamino, dialkylamino, nitro or halo.

It has surprisingly been found by the inventors that compounds of the general formulae I and II:



(I)

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in which

R₁, R₂, W, A, B, Z and Z_A are as defined above have particular utility and effectiveness in the treatment, prophylaxis, amelioration defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buerger's Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; atherosclerosis; Alzheimer's disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohn's disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts.

Thus according to another aspect of the present invention there is provided a method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buerger's Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; atherosclerosis; Alzheimer's disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohn's disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern

- 9 -

baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (for convenience hereafter referred to as the "therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds of formulae I and II as defined above.

Yet another aspect of the present invention is the use of compounds of formulae I and II for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

Still another aspect of the present invention is the use of one or more compounds of formulae I and II in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

And another aspect of the present invention comprises an agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications which comprises one or more compounds of formulae I and II either alone or in association with one or more carriers or excipients.

A further aspect of the invention is a therapeutic composition which comprises one or more compounds of formulae I and II in association with one or more pharmaceutical carriers and/or excipients.

A still further aspect of the present invention is a drink or food-stuff, which contains one or more compounds of formulae I and II.

Another aspect of the present invention is a microbial culture or a food-stuff containing one or more microbial strains which microorganisms produce one or more compounds of formulae I and II.

- 10 -

Still another aspect of the present invention relates to one or more microorganisms which produce one or more compounds of formulae I and II. Preferably the microorganism is a purified culture, which may be admixed and/or administered with one or more other cultures which product compounds of formulae I and II.

5

Throughout this specification and the claims which follow, unless the text requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

10

The term "alkyl" is taken to mean both straight chain and branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tertiary butyl, and the like.

The alkyl group has 1 to 10 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably methyl, ethyl propyl or isopropyl. The alkyl group may optionally be

15

substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkylamino-carbonyl, di-(C₁-C₄-alkyl)-amino-carbonyl, hydroxyl, C₁-C₄-alkoxy, formyloxy, C₁-C₄-alkyl-carbonyloxy, C₁-C₄-alkylthio, C₃-C₆-cycloalkyl or phenyl.

20

The term "aryl" is taken to include phenyl and naphthyl and may be optionally substituted by one or more C₁-C₄-alkyl, hydroxy, C₁-C₄-alkoxy, carbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkylcarbonyloxy or halo.

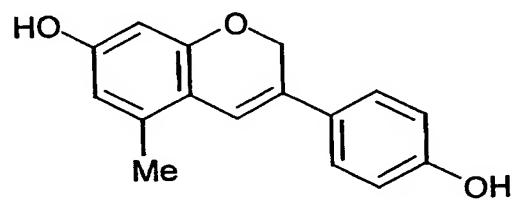
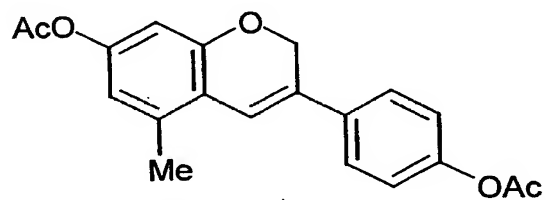
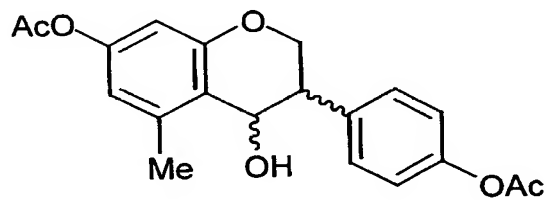
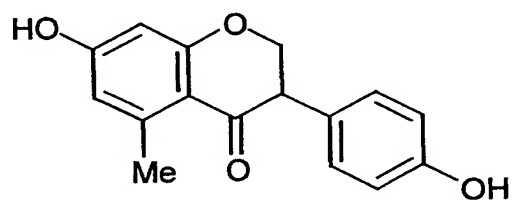
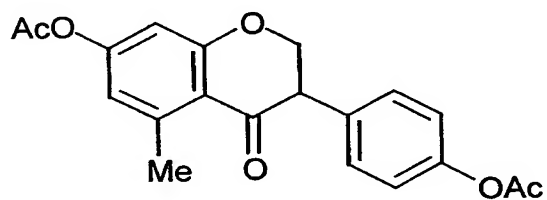
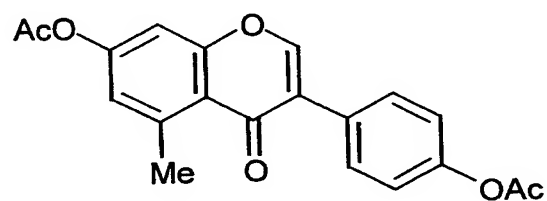
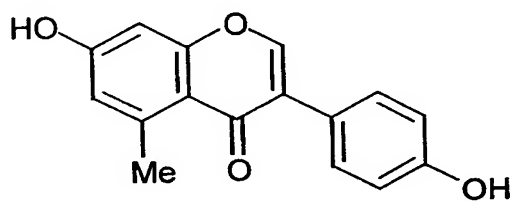
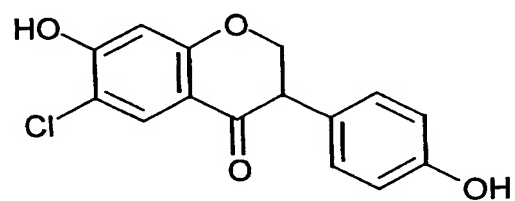
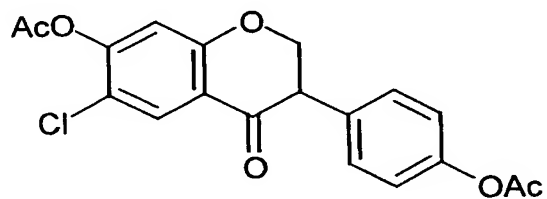
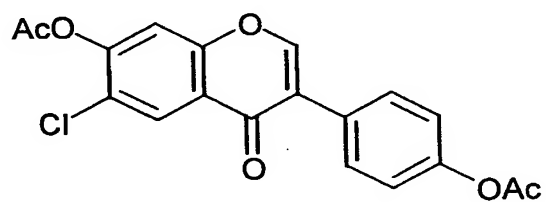
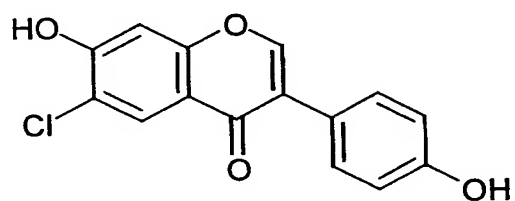
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The term "halo" is taken to include fluoro, chloro, bromo and iodo, preferably fluoro and chloro, more preferably fluoro. Reference to for example "haloalkyl" will include monohalogenated, dihalogenated and up to perhalogenated alkyl groups. Preferred haloalkyl groups are trifluoromethyl and pentafluoroethyl.

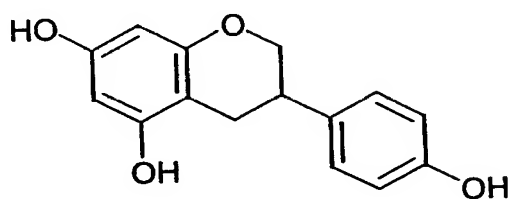
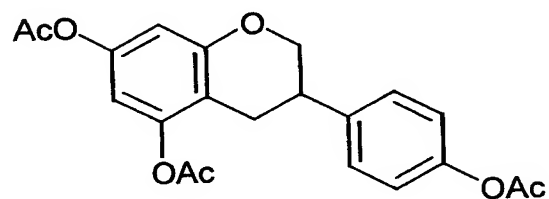
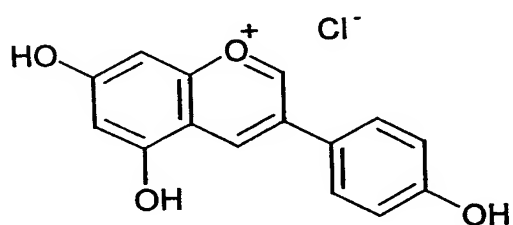
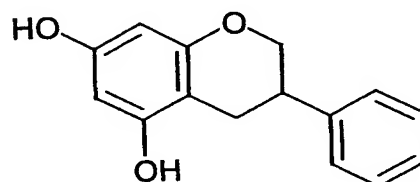
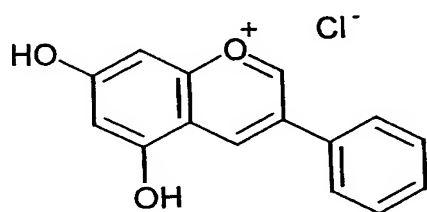
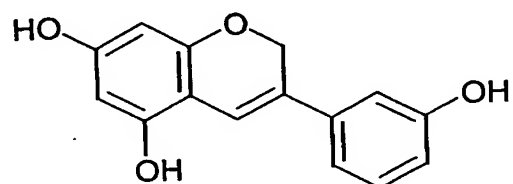
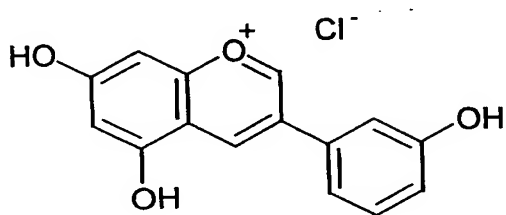
Particularly preferred compounds of the present invention are selected from:

30

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- 12 -



Compounds of the present invention have particular application in the treatment of
5 diseases associated with or resulting from estrogenic effects, androgenic effects,
vasodilatory and spasmodic effects, inflammatory effects and oxidative effects.

The amount of one or more compounds of formulae I and II which is required in a therapeutic treatment according to the invention will depend upon a number of factors, which include the specific application, the nature of the particular compound used, the condition being treated, the mode of administration and the condition of the patient.

5 Compounds of formulae I or II may be administered in a manner and amount as is conventionally practised. See, for example, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 1299 (7th Edition, 1985). The specific dosage utilised will depend upon the condition being treated, the state of the subject, the route of administration and other well known factors as indicated above. In general, a daily dose per patient may be in
10 the range of 0.1 mg to 2 g; typically from 0.5 mg to 1 g; preferably from 50 mg to 200 mg.

The production of pharmaceutical compositions for the treatment of the therapeutic indications herein described are typically prepared by admixture of the compounds of the invention (for convenience hereafter referred to as the "active compounds") with one or
15 more pharmaceutically or veterinarily acceptable carriers and/or excipients as are well known in the art.

The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the subject. The carrier or
20 excipient may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose, for example, a tablet, which may contain from 0.5% to 59% by weight of the active compound, or up to 100% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially
25 of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, optical, buccal (for example, sublingual), parenteral (for example, subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any

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given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

5 Formulation suitable for oral administration may be presented in discrete units, such as capsules, sachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more
10 accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture such as to form a unit dosage. For example, a tablet may be prepared by compressing or moulding a powder or granules containing the active compound, optionally with one or
15 more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound of the free-flowing, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

20

Formulations suitable for buccal (sublingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

25

Compositions of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compounds, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by
30 means of subcutaneous, intramuscular, or intradermal injection. Such preparations may

- 15 -

conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Injectable formulations according to the invention generally contain from 0.1% to 60% w/v of active compound and are administered at a rate of 0.1 ml/minute/kg.

5

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

10

Formulations or compositions suitable for topical administration to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combination of two or more thereof. The active compound is generally present at a concentration of from 0.1% to 0.5% w/w, for example, from 0.5% to 2% w/w. Examples of such compositions include cosmetic skin creams.

15

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered aqueous solution of, for example, 0.1 M to 0.2 M concentration with respect to the said active compound.

20

Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, *Pharmaceutical Research* 3 (6), 318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis/tris buffer (pH 6) or ethanol/water and contain from 0.1 M to 0.2 M active ingredient.

25

- 16 -

The active compounds may be provided in the form of food stuffs, such as being added to, admixed into, coated, combined or otherwise added to a food stuff. The term food stuff is used in its widest possible sense and includes liquid formulations such as drinks including dairy products and other foods, such as health bars, desserts, etc. Food formulations containing compounds of the invention can be readily prepared according to standard practices.

Compounds of the present invention have potent antioxidant activity and thus find wide application in pharmaceutical and veterinary uses, in cosmetics such as skin creams to prevent skin ageing, in sun screens, in foods, health drinks, shampoos, and the like.

It has surprisingly been found that compounds of the formulae I or II interact synergistically with vitamin E to protect lipids, proteins and other biological molecules from oxidation.

Accordingly a further aspect of this invention provides a composition comprising one or more compounds of formulae I or II, vitamin E, and optionally a pharmaceutically, veterinarily or cosmetically acceptable carriers and/or excipients.

Therapeutic methods, uses and compositions may be for administration to humans or animals, such as companion and domestic animals (such as dogs and cats), birds (such as chickens, turkeys, ducks), livestock animals (such as cattle, sheep, pigs and goats) and the like.

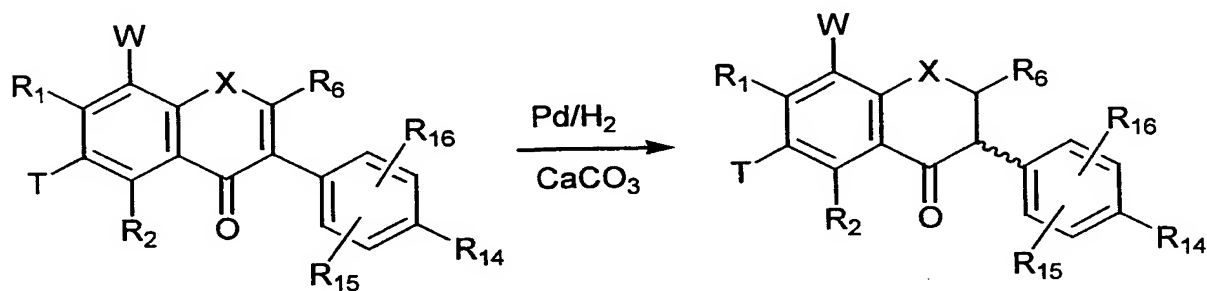
Compounds of formulae I and II may be prepared by standard methods known to those skilled in the art. Suitable methods may be found in, for example, International Patent Application WO 98/08503 which is incorporated herein in its entirety by reference. Methods which may be employed by those skilled in the art of chemical synthesis for constructing the general ring structures depicted in formulae I and II are depicted in schemes 1-8 below. Chemical functional group protection, deprotection, synthons and

- 17 -

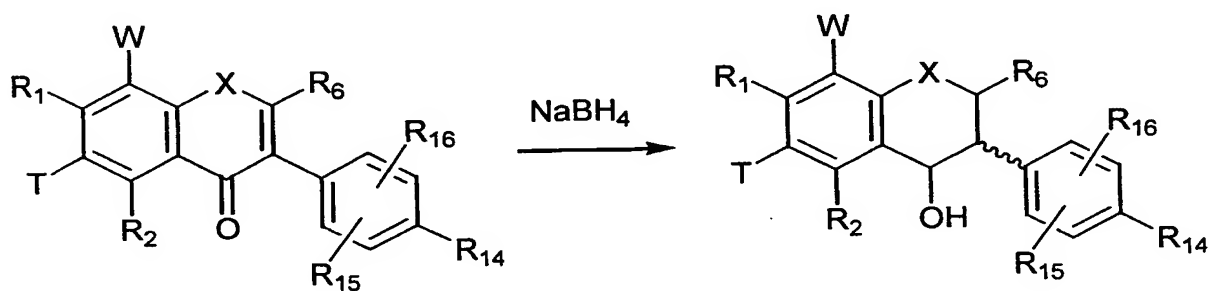
other techniques known to those skilled in the art may be used where appropriate in the synthesis of the compounds of the present invention. In the formulae depicted in the schemes below the moieties R_1 , R_2 , R_6 , R_8 , R_{14} , R_{15} , R_{16} , W and X are as defined above.

The moiety T is either Z or Z_A as defined in formulae I or II above. Reduction of the

- 5 isoflavone derivatives may be effected by procedures well known to those skilled in the art including sodium borohydride reduction, and hydration over metal catalysts such as Pd/C , $Pd/CaCO_3$ and Platinum(IV)oxide (Adam's catalyst) in protic or aprotic solvents. The end products and isomeric ratios can be varied depending on the catalyst/solvent system chosen. The schemes depicted below are not to be considered limiting on the scope of the
- 10 invention described herein.

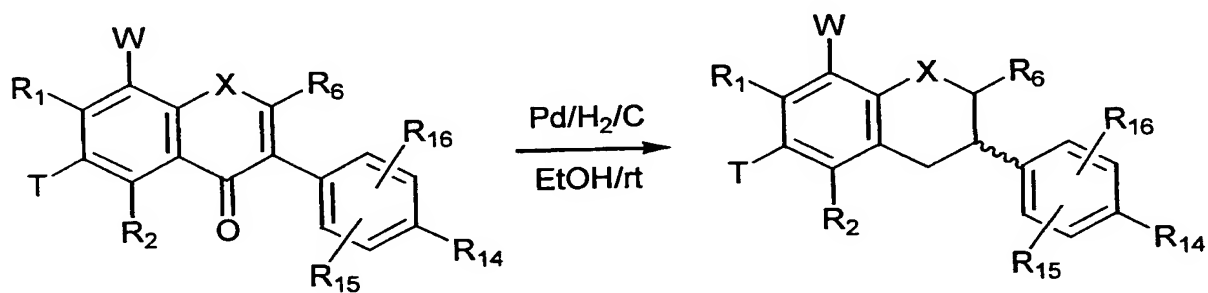


Scheme 1

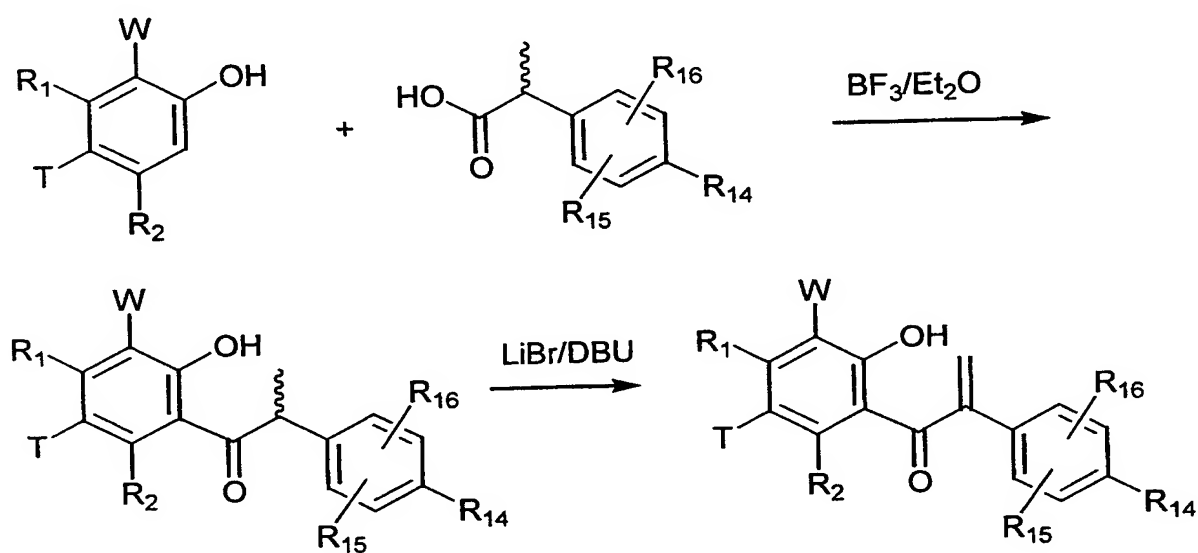


Scheme 2

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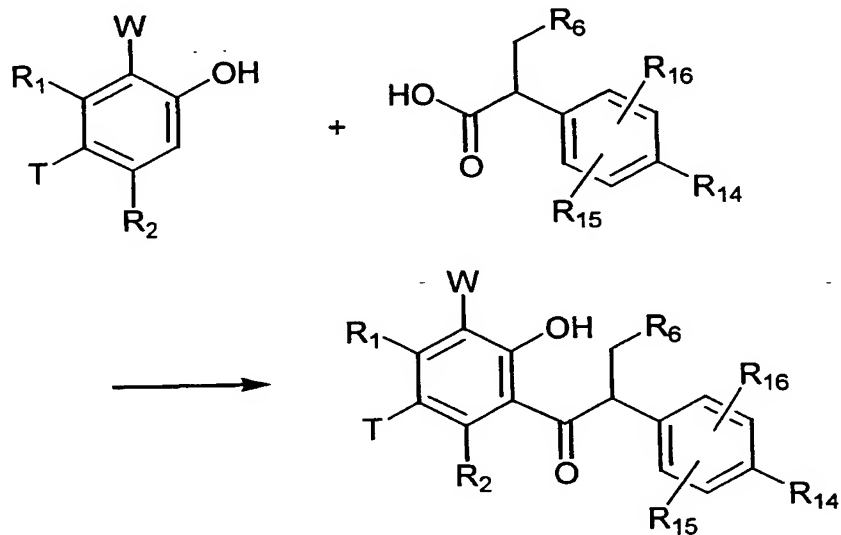


Scheme 3

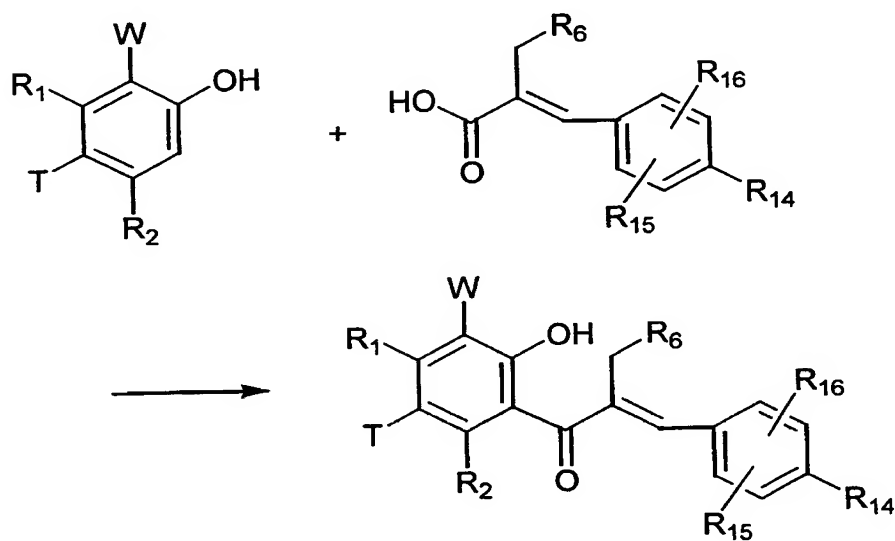


Scheme 4

- 19 -

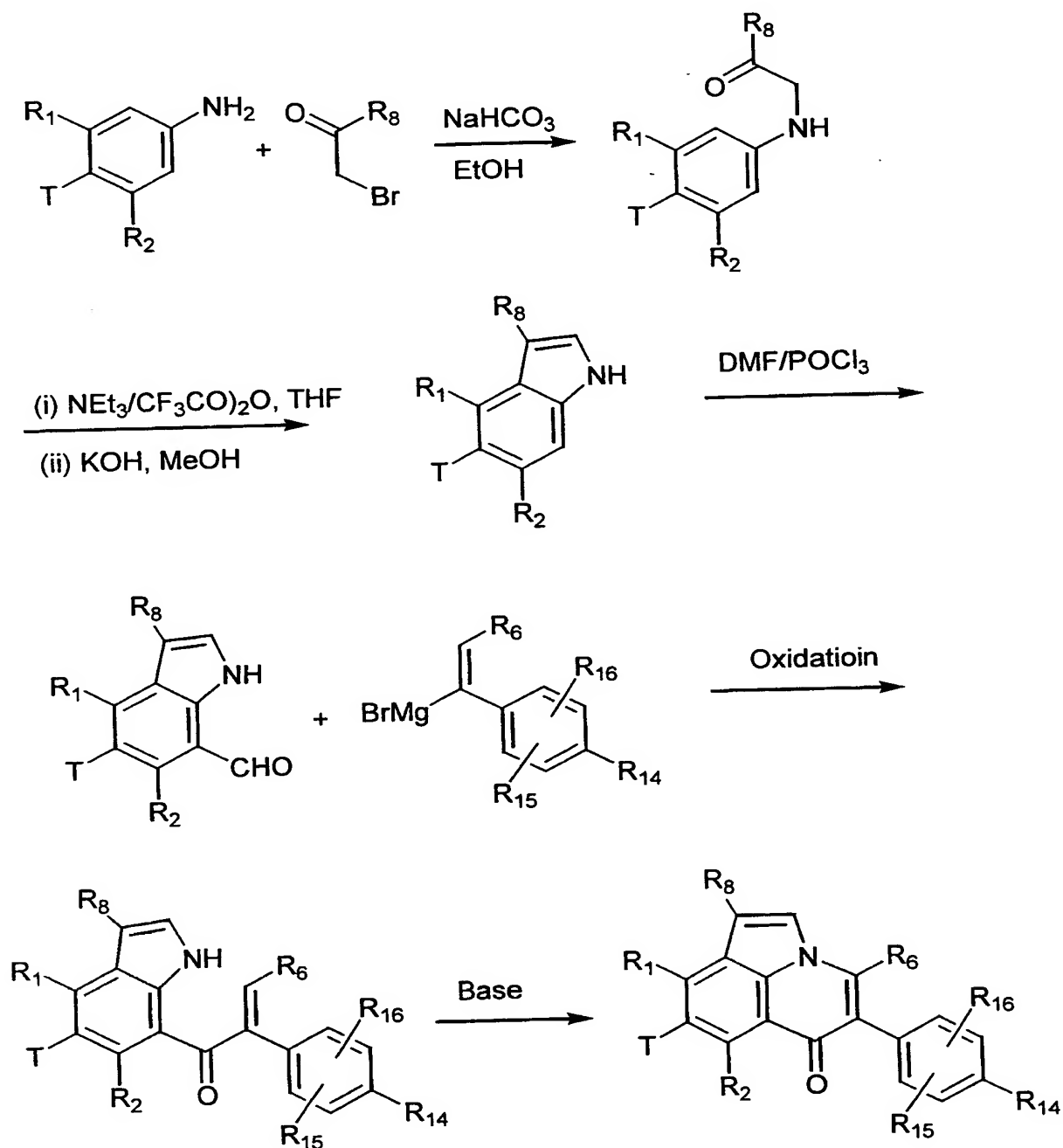


Scheme 5



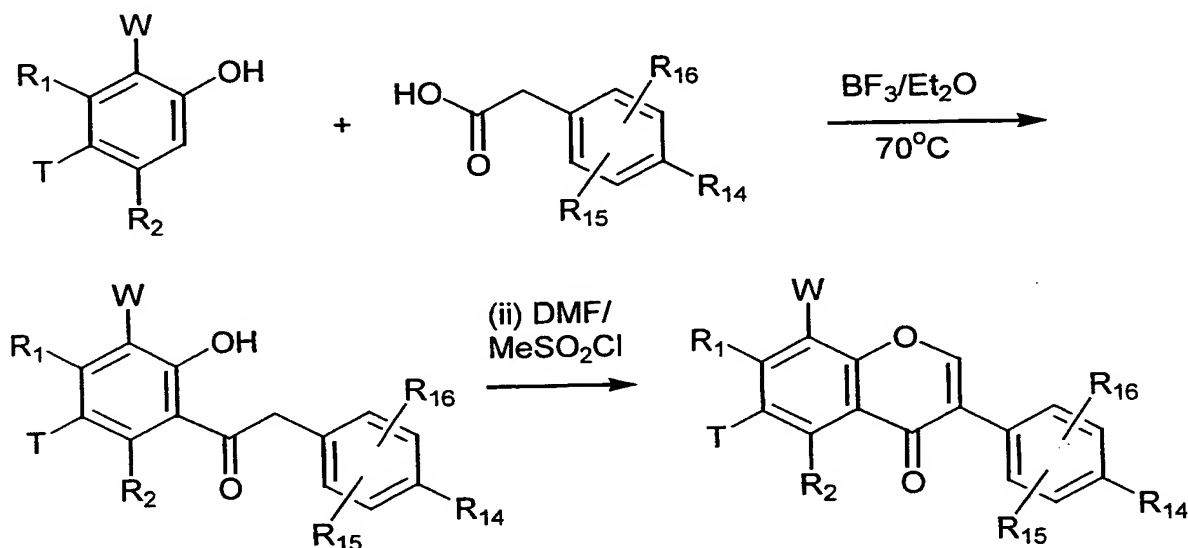
Scheme 6

- 20 -



Scheme 7

- 21 -



Scheme 8

5

EXAMPLE 1**General Syntheses of Substituted Isoflavones**

6-Chloro-4',7-dihydroxyisoflavone was synthesised by the condensation of 4-chlororesorcinol with 4-hydroxyphenylacetic acid to afford 5-chloro-2,4,4'-trihydroxydeoxybenzoin. Cyclisation of the intermediate deoxybenzoin was achieved by treatment with dimethylformamide and methanesulfonyl chloride in the presence of boron trifluoride etherate.

By varying the substitution pattern on the resorcinol or phenylacetic acid groups numerous other substituted isoflavones can also be synthesised in a similar manner. For example starting with 5-methyl resorcinol affords 4',7-dihydroxy-5-methylisoflavone, whilst use of 3-hydroxy phenyl acetic acid in the general synthetic method affords 3'-hydroxy isoflavone derivatives.

20

Isoflavan-4-ones**EXAMPLE 2****Synthesis of 6-Chloro-4',7-diacetoxyisoflavone**

A mixture of 6-chloro-4',7-dihydroxyisoflavone (1.25 g, 4.3 mmol), acetic anhydride (7.5 ml) and pyridine (1.4 ml) was heated in an oil bath at 105-110° C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with aqueous methanol (50%) and dried to yield 6-chloro-4',7-diacetoxyisoflavone (1.2g, 75%) as colourless prisms. ¹H NMR (CDCl₃): δ 2.32 (s, 3H, OCOCH₃), 2.41 (s, 3H, OCOCH₃), 7.16 (d, 2H, J 8.6 Hz, ArH), 7.36 (s, 1H, H8), 7.57 (d, 2H, J 8.6 Hz, ArH), 8.00 (s, 1H, H5), 8.37 (s, 1H, H2).

EXAMPLE 3**Synthesis of 6-Chloro-4',7-diacetoxyisoflavan-4-one**

Adam's catalyst (0.045g) was added to a solution of 6-chloro-4',7-diacetoxyisoflavone (0.25g, 0.7 mmol) in ethyl acetate (30 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 24h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from ethanol to yield 6-chloro-4',7-diacetoxyisoflavan-4-one (0.15g, 60%) as colourless plates. ¹H NMR (CDCl₃): δ 2.29 (s, 3H, OCOCH₃), 2.37 (s, 3H, OCOCH₃), 3.98 (dd, 1H, J 6.0 Hz, 7.5 Hz, H3), 4.68 (m, 2H, H2), 6.87 (s, 1H, H8), 7.07 (d, 2H, J 8.6 Hz, ArH), 7.27 (d, 2H, J 8.6 Hz, ArH), 8.01 (s, 1H, H5).

EXAMPLE 4**Synthesis of 6-Chloro-4',7-dihydroxyisoflavan-4-one**

Imidazole (0.60g) was added to a suspension of 6-chloro-4',7-diacetoxyisoflavan-4-one (0.24g, 0.06 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting precipitate was filtered, washed with water and dried to yield 6-chloro-4',7-

- 23 -

dihydroxyisoflavan-4-one (0.14g, 75%) as a white powder. ^1H NMR (d_6 -acetone): δ 3.87 (t, 1H, J 7.2 Hz, H3), 4.64 (d, 2H, J 6.2 Hz, H2), 6.59 (s, 1H, H8), 6.78 (d, 2H, J 8.7 Hz, ArH), 7.10 (d, 2H, J 8.7 Hz, ArH), 7.70 (bs, 1H, OH), 7.77 (s, 1H, H5).

5 EXAMPLE 5

Synthesis of 4',7-Diacetoxy-5-methylisoflavone

A mixture of 4',7-dihydroxy-5-methylisoflavone (1.51g, 5.6 mmol), acetic anhydride (9 ml) and pyridine (1.7 ml) was heated in an oil bath at 105-110°C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with water and recrystallised from methanol to yield 4',7-diacetoxy-5-methylisoflavone as colourless prisms (1.8g, 91%). m.p. 195-97°C, ^1H NMR (CDCl_3): δ 2.32 (s, 3H, OCOCH_3), 2.35 (s, 3H, OCOCH_3), 2.87 (s, 3H, Me), 6.92 (bs, 1H, H8), 7.12 (bs, 1H, H5), 7.16 (d, 2H, J 8.7 Hz, ArH), 7.55 (d, 2H, J 8.7 Hz, ArH), 7.89 (s, 1H, H2).

15

EXAMPLE 6

Synthesis of 4',7-Diacetoxy-5-methylisoflavan-4-one

Palladium on barium sulfate (5%, 0.06g) was added to a solution of 4',7-diacetoxy-5-methylisoflavone (0.30g, 0.8 mmol) in ethyl acetate (50 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 24h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from ethanol to yield 4',7-diacetoxy-5-methylisoflavan-4-one (0.20g, 67%) as colourless plates. m.p. 143-45°C, ^1H NMR (CDCl_3): δ 2.29 (s, 3H, OCOCH_3), 2.30 (s, 3H, OCOCH_3), 2.62 (s, 3H, Me), 3.95 (t, 1H, J 7.2 Hz, H3), 4.62 (d, 2H, J 6.8 Hz, H2), 6.59 (d, 1H, J 2.2 Hz, H8), 6.66 (d, 1H, J 2.2 Hz, H5), 7.07 (d, 2H, J 8.3 Hz, ArH), 7.28 (d, 2H, J 8.3 Hz, ArH).

30

EXAMPLE 7**Synthesis of 4',7-Dihydroxy-5-methylisoflavanone**

Imidazole (0.63g) was added to a suspension of 4',7-diacetoxy-5-methylisoflavan-4-one (0.50g, 1.4 mmol) in absolute ethanol (20.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting precipitate was filtered, washed with water and dried to yield 4',7-dihydroxy-5-methylisoflavan-4-one (0.25g, 66%) as a white powder. ¹H NMR (d₆-acetone): δ 2.51 (s, 3H, Me), 3.76 (t, 1H, J 5.7 Hz, H3), 4.57 (d, 2H, J 7.1 Hz, H2), 6.26 (d, 1H, J 2.2 Hz, H8), 6.35 (d, 1H, J 2.2 Hz, H5), 6.78 (d, 2H, J 8.7 Hz, ArH), 7.11 (d, 2H, J 8.7 Hz, ArH).

Isolflavan-4-ols and Isoflav-3-enes**EXAMPLE 8****Synthesis of 4'-7-Diacetoxy-5-methylisoflavan-4-ol**

4'-7-Diacetoxy-5-methylisoflavan-4-ol was prepared by the reduction of 4'-7-diacetoxy-5-methylisoflavone (0.25g) with Adam's catalyst in ethyl acetate (30 ml) under a hydrogen atmosphere for 72 hours. The solution was filtered through a pad of Celite to yield predominantly *cis*-4'-7-diacetoxy-5-methylisoflavan-4-ol. ¹H NMR (CDCl₃): δ 2.26 (s, 3H, OCOCH₃), 2.30 (s, 3H, OCOCH₃), 2.62 (s, 3H, Me), 3.24 (dt, 1H, J 3.4 Hz, J 11.8 Hz, H3), 4.31 (ddd, 1H, J 1.4 Hz, 3.6 Hz, 10.5 Hz, H2); 4.57 (dd, 1H, J 10.5 Hz, 11.8 Hz, H2), 4.82 (bs, 1H, H4), 6.51 (d, 1H, J 2.1 Hz, H8), 6.59 (d, 1H, J 2.1 Hz, H6), 7.06 (d, 2H, J 8.6 Hz, ArH), 7.29 (d, 2H, J 8.6 Hz ArH).

EXAMPLE 9**25 Synthesis of 4',7-Diacetoxy-5-methylisoflav-3-ene**

4',7-Diacetoxy-5-methylisoflav-3-ene was prepared by the dehydration of *cis*- and *trans*-4'-7-diacetoxy-5-methylisoflavan-4-ol (0.2g) with phosphorus pentoxide (2.0g) in dry dichloromethane (20 ml). The crude product was chromatographed on silica column using dichloromethane as the eluent. ¹H NMR (CDCl₃): δ 2.28 (s, 3H, OCOCH₃), 2.31 (s, 3H,

- 25 -

OCOCH₃), 2.36 (s, 3H, Me), 5.08 (s, 2H, H₂), 6.49 (d, 1H, J 2.0 Hz, H₈), 6.52 (d, 1H, J 2.2 Hz, H₅), 6.89 (s, 1H, H₄), 7.14 (d, 2H, J 8.6 Hz, ArH), 7.44 (d, 2H, J 8.6 Hz, ArH).

EXAMPLE 10**5 Synthesis of 4',7-Dihydroxy-5-methylisoflav-3-ene**

4',7-Dihydroxy-5-methylisoflav-3-ene was prepared from 4',7-diacetoxy-5-methylisoflav-3-ene by the removal of the acetoxy groups by hydrolysis under standard conditions.

EXAMPLE 11**10 Synthesis of 3',5,7-Trihydroxyisoflavylum chloride**

Phosphoryl chloride (1.75 ml) was added to a mixture of the monoaldehyde (0.95g) and phloroglucinol dihydrate (1.6g) in acetonitrile (10 ml). The mixture was stirred at 30°C for 20 minutes and then at room temperature for 3 hours. The orange precipitate was filtered and washed with acetic acid to yield the isoflavylum salt.

15

EXAMPLE 12**Synthesis of Isoflav-3-ene-3',5,7-triol**

Isoflav-3-ene-3',5,7-triol was prepared by the reduction of 3',5,7-trihydroxyisoflavylum chloride (0.5g) with sodium cyanoborohydride (0.33g) in ethyl acetate (11 ml) and acetic acid (3 ml) and chromatographic separation of the resulting mixture of isoflav-3-ene and isoflav-2-ene mixture. ¹H NMR (d₆-acetone): δ 4.99 (s, 2H, H₂), 5.92 (d, 1H, J 2.0 Hz, ArH), 6.04 (d, 1H, J 2.2 Hz, ArH), 6.78-7.18 (m, 5H, ArH).

20

*Isoflavans***25 EXAMPLE 13****Synthesis of Isoflavan-5,7-diol**

Isoflavan-5,7-diol was prepared by the reduction of a suspension of 5,7-dihydroxyisoflavylum chloride (0.5g) with Palladium-on-charcoal (5%, 0.1g) in acetic acid (15 ml) containing ethyl acetate (2.5 ml) under a hydrogen atmosphere. The crude

- 26 -

product was recrystallised from 1,2-dichloromethane to give the isoflavan as colourless needles, m.p. 76-78°C (lit m.p. 77-79°C).

EXAMPLE 14

5 Synthesis of 4',5,7-Triacetoxyisoflavan

4',5,7-Triacetoxyisoflavan was prepared by the reduction of a suspension of 4',5,7-trihydroxyisoflavylum chloride (0.31g) with platinum oxide (0.04g) in a mixture of acetic anhydride (2.0 ml) and ethyl acetate (10 ml) under a hydrogen atmosphere. After the removal of catalyst the crude product was refluxed with pyridine (0.5 ml) and the resulting
10 triacetate was isolated by evaporation of the solvent and crystallisation of the residue. M.p. 126-28°C.

EXAMPLE 15

Synthesis of Isoflavan-4',5,7-triol

15 Isoflavan-4',5,7-triol was prepared from 4',5,7-triacetoxyisoflavan by the removal of the acetyl groups by hydrolysis. M.p. 206-8°C.

EXAMPLE 16

The binding affinity of various compounds of the invention for both subtypes of the
20 estrogen receptor was determined with the "Estrogen Receptor Alpha or Beta Competitor Assay Core HTS Kit" supplied by Panvera Corporation (Product No. P2614/2615). 6-Chloro-4',7-dihydroxyisoflavan-4-one showed good competitive binding to the estrogen receptor with the following results:

25 ER alpha receptor = 37.82 uM
ER beta receptor = 32.14 uM

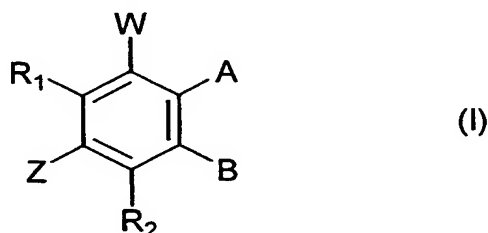
The results show that the compounds of the present invention have particular application in the treatment of diseases associated with or resulting from estrogenic effects, androgenic
30 effects, vasodilatory and spasmodic effects, inflammatory effects and oxidative effects.

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Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The inventions also includes all of the steps, features, compositions and compounds referred to or indicated in
5 the specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

The claims defining the invention are as follows:

1. An isoflavone compound or analogue thereof of the general formula I:

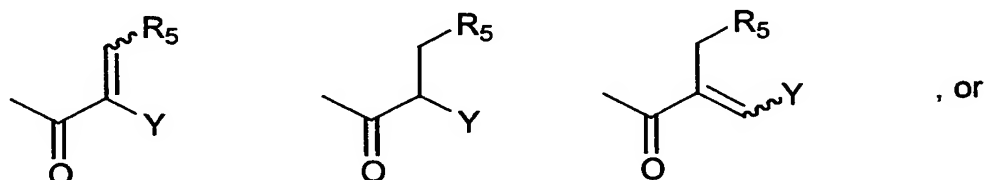


- 5 in which

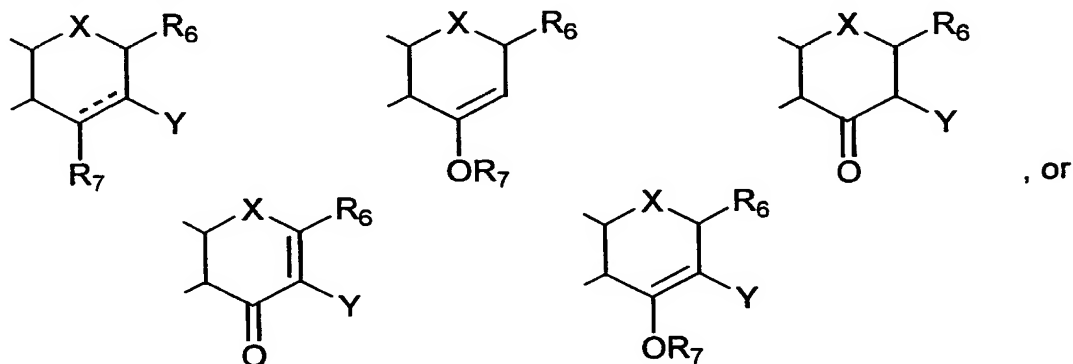
R_1 and R_2 are independently hydrogen, hydroxy, OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO , $C(O)R_{10}$, $COOH$, CO_2R_{10} , $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

Z is hydrogen, and

- 10 W is R_1 , A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

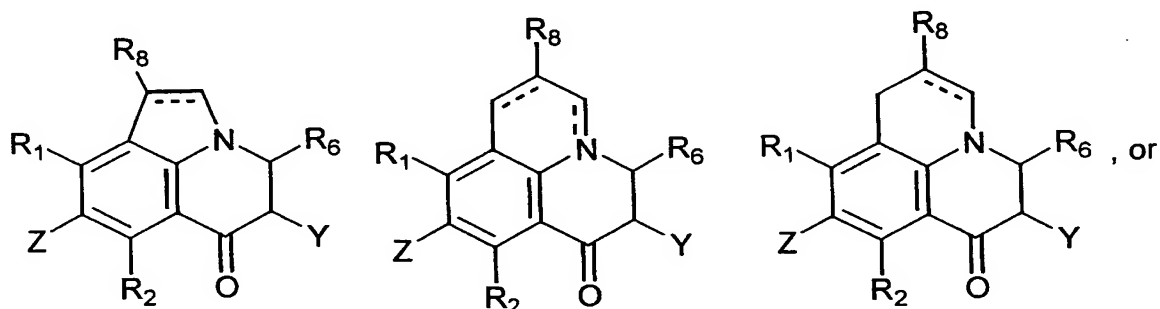


W is R_1 , and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from

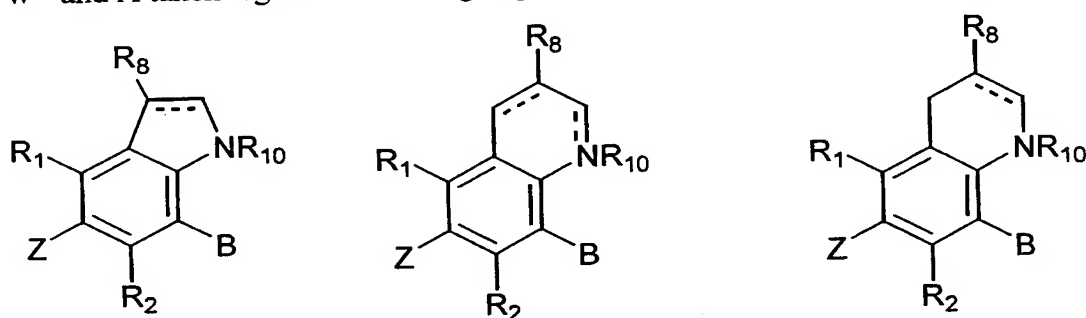


- 15 W , A and B taken together with the groups to which they are associated comprise

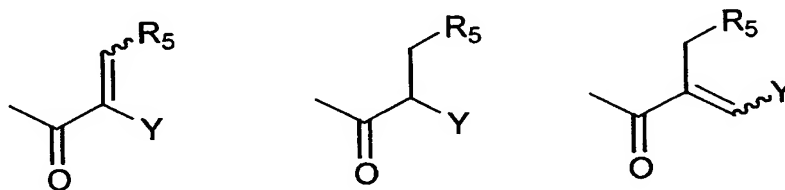
- 29 -



W and A taken together with the groups to which they are associated comprise



and B is



5

wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen, alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

10 R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

15 R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4 , COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

- 30 -

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

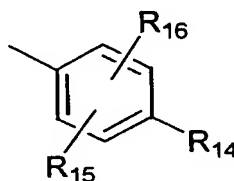
R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or

5 dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



10 wherein

R_{14} , R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10} , $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that

15 when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

W is hydrogen, then

20 Y is not 4-hydroxyphenyl or 4-alkylphenyl;

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as

25 previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, then

W is not hydrogen;

- 31 -

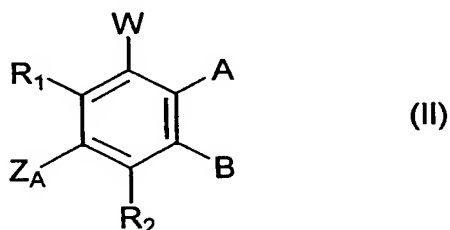
when

- R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and
 Y is 4-hydroxyphenyl or 4-alkylphenyl, and
 W is hydrogen, then
 5 R_2 is not hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined; and

when

- R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as
 10 previously defined, and
 Y is 4-hydroxyphenyl or 4-alkylphenyl, and
 W is hydrogen, then
 R_1 is not hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid.

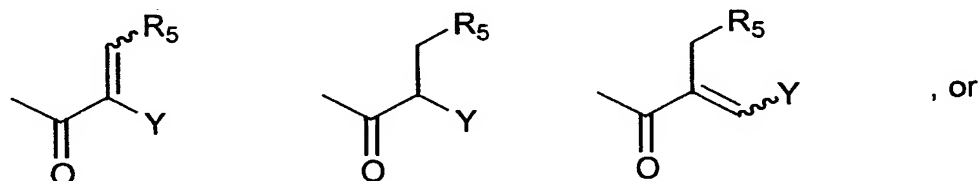
- 15 2. An isoflavone compound or analogue thereof of the general formula II:



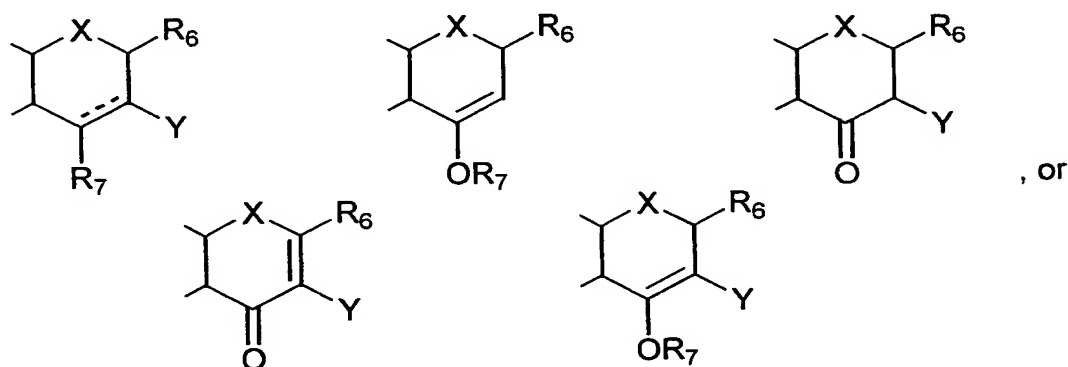
in which

- R_1 and R_2 are independently hydrogen, hydroxy, OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO,
 20 $C(O)R_{10}$, COOH, CO_2R_{10} , $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio,
 amino, alkylamino, dialkylamino, nitro or halo,
 Z_A is OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10} , $CONR_3R_4$, alkyl,
 haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or
 halo, and
 25 W is R_1 , A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

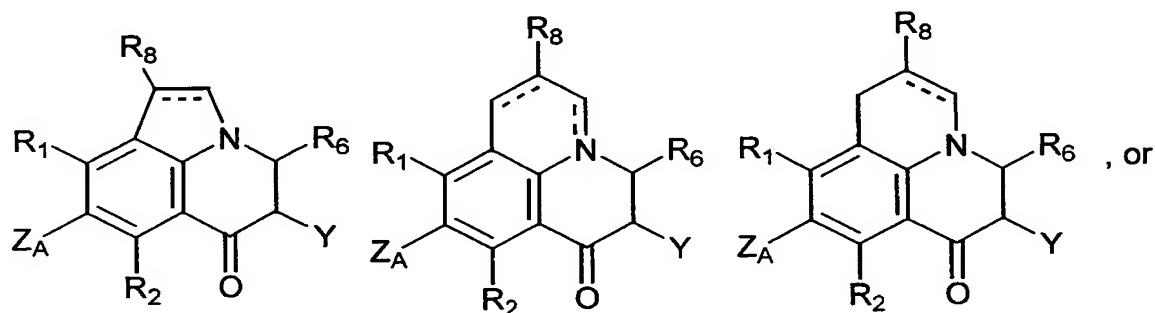
- 32 -



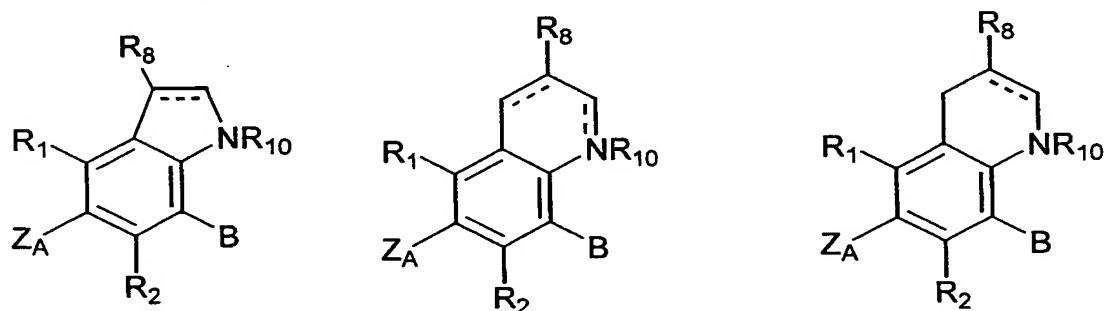
W is R₁, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from



5 W, A and B taken together with the groups to which they are associated comprise

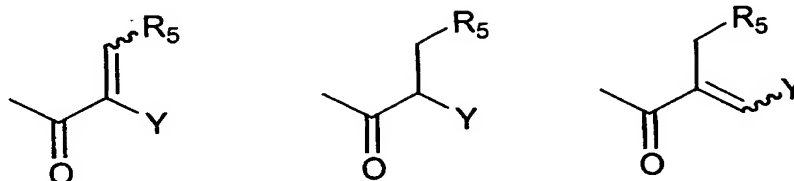


W and A taken together with the groups to which they are associated comprise



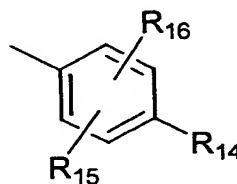
and B is

- 33 -



wherein

- R₃ is hydrogen, alkyl, aryl, arylalkyl, an amino acid, C(O)R₁₁ where R₁₁ is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO₂R₁₂ where R₁₂ is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,
- R₄ is hydrogen, alkyl or aryl, or R₃ and R₄ taken together with the nitrogen which they are attached are pyrrolidinyl or piperidinyl,
- R₅ is hydrogen, C(O)R₁₁ where R₁₁ is as previously defined, or CO₂R₁₂ where R₁₂ is as previously defined,
- R₆ is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR₃R₄, COR₁₁ where R₁₁ is as previously defined, CO₂R₁₂ where R₁₂ is as previously defined or CONR₃R₄,
- R₇ is hydrogen, C(O)R₁₁ where R₁₁ is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or Si(R₁₃)₃ where each R₁₃ is independently hydrogen, alkyl or aryl,
- R₈ is hydrogen, hydroxy, alkoxy or alkyl,
- R₉ is alkyl, haloalkyl, aryl, arylalkyl, C(O)R₁₁ where R₁₁ is as previously defined, or Si(R₁₃)₃ where R₁₃ is as previously defined,
- R₁₀ is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,
- the drawing "---" represents either a single bond or a double bond,
- X is O, NR₄ or S, and
- Y is

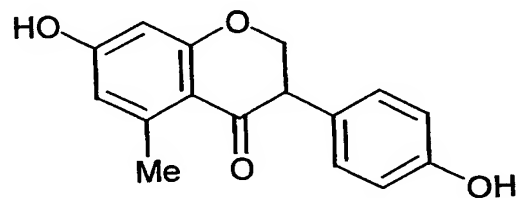
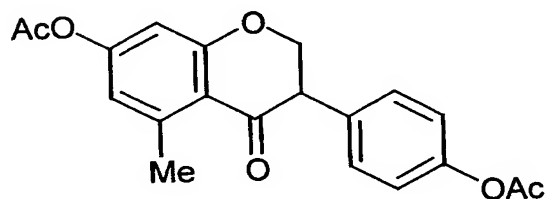
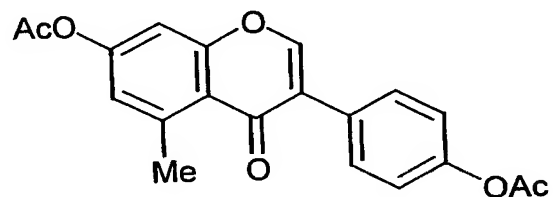
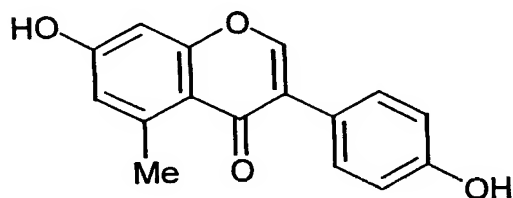
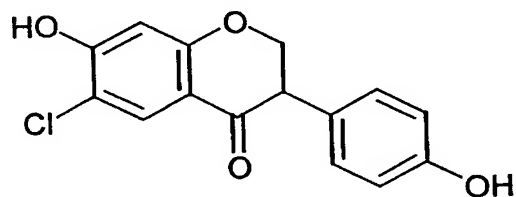
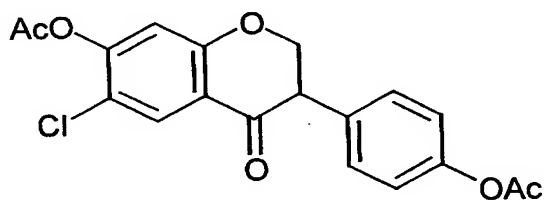
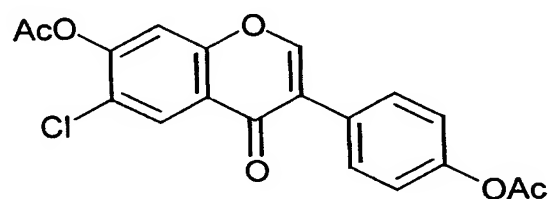
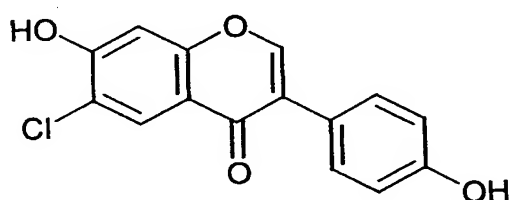


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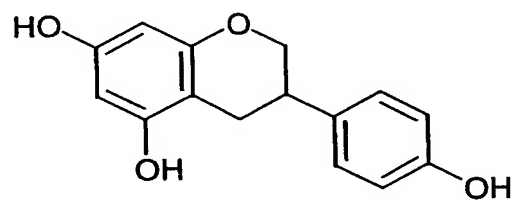
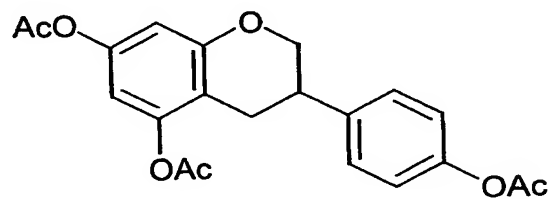
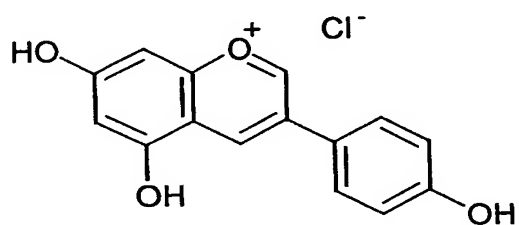
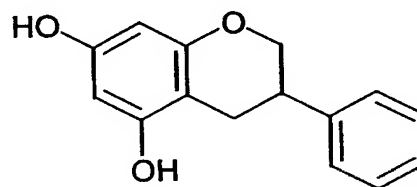
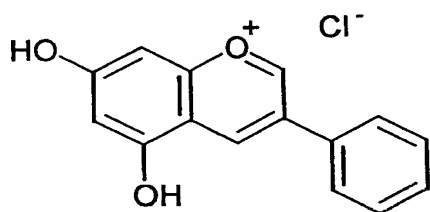
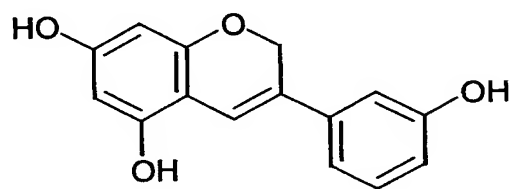
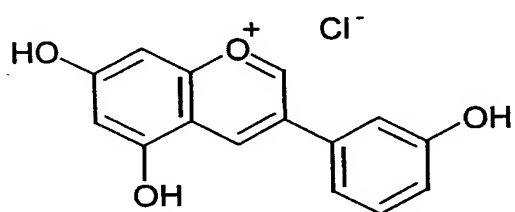
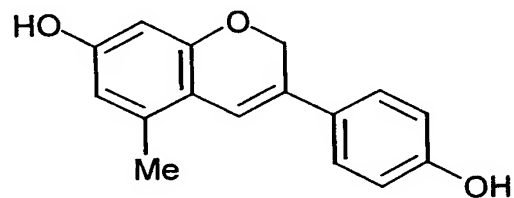
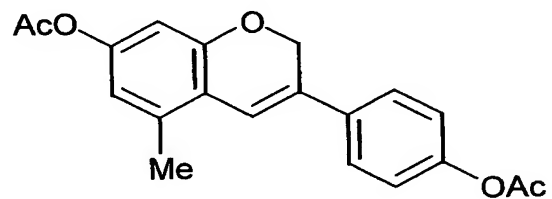
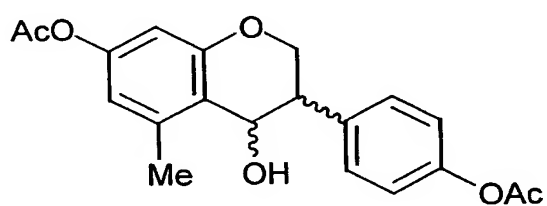
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R_{14} , R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9 , $OC(O)R_{10}$, $OS(O)R_{10}$, CHO , $C(O)R_{10}$, $COOH$, CO_2R_{10} , $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo.

- 5 3. A compound of formulae I as defined in claim 1 or of formula II as defined in claim 2 selected from the group consisting of:



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4. A method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buerger's Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; arteriosclerosis; Alzheimer's disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohn's disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (the "therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds selected from formulae I and II.

5. Use of one or more compounds selected from formulae I and II for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more therapeutic indications according to claim 4.

6. Use of one or more compounds selected from formulae I and II in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more therapeutic indications according to claim 4.

7. An agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications according to claim 4 which comprises one or more compounds selected from formulae I and II either alone or in association with one or more carriers or excipients.

8. A therapeutic composition which comprises one or more compounds selected from formulae I and II in association with one or more pharmaceutical carriers and/or excipients.

5 9. A drink or food-stuff, which contains one or more compounds selected from formulae I and II.

10 10. A microbial culture or a food-stuff containing one or more microbial strains which microorganisms produce one or more compounds selected from formulae I and II.

15 11. One or more microorganisms which produce one or more compounds selected from formulae I and II.

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